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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/579,338	NISHIDA ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

In response to the Non-Final Office Action dated 11/21/08, applicants' response filed on 02/18/09 is acknowledged. In said response, applicants' amended claims 1-4 and added a new claim 18.

Claims 1-18 are pending, claims 9-17 remain withdrawn as said claims are drawn to non-elected inventions. Thus claims 1-8 and 18 are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Priority

This application is a 371 of PCT/JP04/16297 filed on 11/04/2004 and claims the priority date of Japanese applications 2003-388165 filed on 11/18/2003 and 2004-165919 filed on 06/03/2004. Examiner notes that the applicants' have provided certified copies of Japanese applications 2003-388165 filed on 11/18/2003 and 2004-165919 filed on 06/03/2004, however no English translation of said applications have been provided. Furthermore, examiner for the record would like to reiterate that the elected sequence information is missing in PCT/JP04/16297 application copy as submitted by the applicants' with the instant application. However, as directed by the applicants' in their response dated 02/18/09, examiner was able to find the elected sequence information in the WIPO document, WO/2005/049643 of International Application No.: PCT/JP2004/016297 filed on 11/04/2004 (see enclosed printout of the WIPO document). Therefore, the priority date for instant claims under consideration is

deemed to be the filing date of International Application No.: PCT/JP2004/016297 filed on 11/04/2004.

Withdrawn-Claim Rejections: 35 USC § 101

Previous rejection of claims 1 and 2, rejected under 35 U.S.C. 101, is being withdrawn due to amendments to claims.

Withdrawn- Claim Rejections 35 USC § 112-Second Paragraph

Previous rejection of claims 1 and 2 and claims 3-8 depending therefrom, rejected under 35 U.S.C. 112, second paragraph, is being withdrawn due to amendments to claims.

Withdrawn-Claim Rejections 35 USC § 102

Previous rejections of claims 1-8 rejected under 35 U.S.C. 102(a) as being anticipated by Nishida et al., (Appl. Environ. Microbiol., 2005, Vol. 71 (8): 4286-4296 in IDS) and claims 1-8 rejected under 35 U.S.C. 102(a) as being anticipated by Tao et al., (Gene, 2006, Vol. 379; 101-108, available online 05/03/2006), are being withdrawn due to grant of proper priority date for the elected sequence. Note, examiner was able to find the elected sequence information in the WIPO document, WO/2005/049643 of International Application No.: PCT/JP2004/016297 filed on 11/04/2004 (see enclosed printout of the WIPO document). Therefore, the priority date for instant claims under `consideration is deemed to be the filing date of International Application No.: PCT/JP2004/016297 filed on 11/04/2004.

Claim Objections

Claim 18 is objected, due to the following informality: Claim 18 recites "FPP" abbreviation in the claim. Examiner suggests at least in the first recitation of the

abbreviation, expanding the term to recite the full form of what the abbreviation stands for. Appropriate correction is required. For examination purposes, examiner interprets abbreviation/term "FPP" stands for farnesyl pyrophosphate (page 17 of specification).

Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Maintained-Enablement

Claims 1 and 2 and claims 3-8 and 18 depending therefrom are rejected under 35 U.S.C. 112, first paragraph, because the specification is being enabling for an isolated polypeptide of SEQ ID NO: 4 having β-ionone ring-2-hydroxylase activity and encoded by a polynucleotide sequence of SEQ ID NO: 3, isolated microorganism comprising said polynucleotide and encoding said polypeptide, said microorganism comprising carotenoid biosynthesis genes comprised in plasmids pAC-Cantha or pAC-Asta, comprising the polynucleotide coding sequences amplifiable from *Brevundimonas* sp. Strain SD-212 nucleic acid (DNA template) by primers comprising the following sequences: *crtE* (SEQ ID NO: 19 and 20), *crtB* (SEQ ID NO: 13 and 14), *crtI* (SEQ ID NO: 11 and 12), *crtY* (SEQ ID NO: 9 and 10) and *crtW* (SEQ ID NO: 7 and 8; page 20 of specification) and to a method for preparing hydroxylated carotenoids by culturing said microorganism, does not reasonably provide enablement for: i) any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a polynucleotide having a nucleotide sequence that hybridizes under

defined stringent conditions to the full-length nucleotide sequence shown in SEQ ID NO: 3 (as in claims 1 and 2); ii) a microorganism comprising said gene and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring (as in claim 3); iii) a microorganism comprising said gene and other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants (as in claims 4-6 and 18); and iv) to a method for preparing hydroxylated carotenoids by culturing said microorganism (as in claims 7 and 8). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-8 and 18 are so broad as to encompass: i) any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of

SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a gene having a nucleotide sequence that hybridizes under defined stringent conditions to the full-length nucleotide sequence shown in SEQ ID NO: 3 (as in claims 1 and 2); ii) a microorganism comprising said gene and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring (as in claim 3); iii) a microorganism comprising said gene and other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants (as in claims 4-6 and 18); and iv) to a method for preparing hydroxylated carotenoids by culturing said microorganism (as in claims 7 and 8).

The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides and encoding nucleotide sequences as broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e.

expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function.

However, in this case the disclosure is limited to making and the use of an isolated polypeptide of SEQ ID NO: 4 having β-ionone ring-2-hydroxylase activity and encoded by a polynucleotide sequence of SEQ ID NO: 3, isolated microorganism comprising said polynucleotide and encoding said polypeptide, said microorganism comprising carotenoid biosynthesis genes comprised in plasmids pAC-Cantha or pAC-Asta, comprising the polynucleotide coding sequences amplifiable from *Brevundimonas* sp. Strain SD-212 nucleic acid (DNA template) by primers comprising the following sequences: *crtE* (SEQ ID NO: 19 and 20), *crtB* (SEQ ID NO: 13 and 14), *crtI* (SEQ ID NO: 11 and 12), *crtY* (SEQ ID NO: 9 and 10) and *crtW* (SEQ ID NO: 7 and 8; page 20 of specification) and to a method for preparing hydroxylated carotenoids by culturing said microorganism, but provides no guidance with regard to the making of variants and mutants of all the claimed peptides and encoding polynucleotides or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed peptides and encoding nucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the peptides and encoding nucleotides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications as required by the instant claims. The specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish even further with additional modification, e.g. multiple substitutions or deletions or insertions or transpositions.

The specification does not support the broad scope of the claims i.e., i) any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a gene having a nucleotide sequence that hybridizes under defined stringent conditions to the full-length nucleotide sequence shown in SEQ ID NO: 3; ii) a microorganism comprising said gene and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring; iii) a microorganism comprising said gene and other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants; and iv) to a method for preparing

hydroxylated carotenoids by culturing said microorganism, as claimed in claims 1-8 and 18, because the specification does not establish: (A) regions of the peptide/nucleotide structure which may be modified without affecting the activity of β-ionone ring-2-hydroxylase activity or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants; (B) the general tolerance of the peptide and the nucleotide encoding the activity of β-ionone ring-2-hydroxylase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the nucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including peptides and encoding nucleotide sequences with an enormous number of modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of peptides and encoding nucleotides i.e., i) any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a gene having a nucleotide sequence that hybridizes under defined stringent conditions to the full-length nucleotide

sequence shown in SEQ ID NO: 3; ii) a microorganism comprising said gene and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring; iii) a microorganism comprising said gene and other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants; and iv) to a method for preparing hydroxylated carotenoids by culturing said microorganism, broadly encompassed by the claims is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection of claims 1-8 and 18 under 35 U.S.C. 112 for enablement be withdrawn, applicants', provide the following argument.

"The specification on page 14 details other genes, which encode proteins having β-ionone ring-2-hydroxylase activity would have at least 50% homology to SEQ ID NO: 4 based on the comparison with other carotenoid proteins and this level of identity would be expected to be present in the enzymes encoded by genes isolated from other organisms" (pages 10-11 of applicants' response dated 02/18/09).

Reply: While as discussed by applicants, the art teaches isolation of other genes having β-ionone ring-2-hydroxylase activity, however as noted by the examiner there is very low homology/identity (SCORE search results) between the peptide sequence of

SEQ ID NO: 4 and other sequences having β-ionone ring-2-hydroxylase activity. The scope of these claims are broad despite the guidance of the art and specification, the claims remain not commensurate in scope with the enabled invention. Examiner finds support for his position in the following scientific teachings:

A) As taught by the art, even highly structurally homologous polypeptides do not necessarily share the same function and many functionally similar proteins will have little or no structural homology to disclosed proteins. For example, proteins having similar structure have different activities (structure does not always correlate to function); Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures.

B) As cited below (written description rejection), neither the prior art at the time of filing of the instant application nor the specification provides information regarding catalytic domains, the binding domains, the core motifs and 3D model or the defined

core regions/motifs involved in the desired biological activity/enzymological characteristics of the polypeptide i.e., β-ionone ring-2-hydroxylase activity, the tertiary structure of the molecule and folding patterns that are essential for the desired biological activity/enzymological characteristics. Therefore, examiner takes the position that due to the paucity of information regarding structure-function correlation, the specification lacks identifying characteristics of all of the sequences within the claimed genus, especially of any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a nucleotide sequence that hybridizes under defined stringent conditions to a nucleotide sequence shown in SEQ ID NO: 3

C) Furthermore, claims 1-8 and 18 as interpreted, are directed to random variant and mutant peptides having β-ionone ring-2-hydroxylase activity and encoded by random mutants and variants of a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 3 and the encoded polypeptide having at least 50% sequence identity to the peptide sequence of SEQ ID NO: 4. The guidance provided by the applicants is limited and especially to an isolated peptide of SEQ ID NO: 4 having β-ionone ring-2-hydroxylase activity and encoded by the polynucleotide of SEQ ID NO: 3. However, random variant and mutant peptides having at least 50% sequence identity to the peptide sequence of SEQ ID NO: 4 said peptides having β-ionone ring-2-hydroxylase activity and encoded by random mutant and variant polynucleotides that hybridize under

defined conditions to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 3, would clearly constitute **undue** experimentation (see scientific support below).

Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the percentage of active mutants for multiple mutations/changes appears to be exponentially related to this by the simple formula $(0.66)^{\wedge x}$ X 100% where **x** is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 50% sequence identity to the peptide sequence of SEQ ID NO: 4 allows up to 129 mutations/changes within the 257 amino acid residues of sequence of SEQ ID NO: 4, thus, only $(0.66)^{\wedge 129}$ X 100% equivalent to $\mathbf{5.26 \times 10^{-22}}$ % of random mutants and variants having 50% sequence identity to SEQ ID NO: 4 would be active. While these calculations are only estimates of the actual situation, they are presented to provide a basis for understanding the examiner's decision on which claim scope would require only routine experimentation and which claim scope would reach a level which is undue. The guidance in the instant case and current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a reasonable number of active mutants within hundred thousand inactive mutants of SEQ ID NO: 4. But finding a few mutants within several trillions or more, would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable

amount of guidance with respect to the direction in which the experimentation should proceed (guided mutants). Such guidance has **not** been provided in the instant specification i.e., information regarding catalytic domains, the binding domains, the core motifs and 3D model or the defined core regions/motifs involved in the desired biological activity/enzymological (β-ionone ring-2-hydroxylase activity), the tertiary structure of the molecule and folding patterns that are essential for the desired biological activity/enzymological characteristics.

It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

Therefore, the specification does not support the broad scope of the claims which encompass i) any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a gene having a nucleotide sequence that hybridizes under defined stringent conditions to the full-length nucleotide sequence shown in SEQ ID NO: 3; ii) a microorganism comprising said gene and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-

ionone ring; iii) a microorganism comprising said gene and other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants; and iv) to a method for preparing hydroxylated carotenoids by culturing said microorganism, as claimed in claims 1-8 and 18, because the specification does not establish: (A) regions of the peptide/nucleotide structure which may be modified without affecting the activity of β-ionone ring-2-hydroxylase activity or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants; (B) the general tolerance of the peptide and the nucleotide encoding the activity of β-ionone ring-2-hydroxylase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the nucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Maintained-Written Description

Claims 1-8 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Claims 1-8 and 18 are rejected under this section 35 U.S.C. 112, because the claims as interpreted, are directed to encompass a genus of polypeptides and encoding polynucleotides i. e., i) any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a gene having a nucleotide sequence that hybridizes under defined stringent conditions to the full-length nucleotide sequence shown in SEQ ID NO: 3; ii) a microorganism comprising said gene and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring; iii) a microorganism comprising said gene and other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon

of β-ionone ring or said microorganism comprising one or more carotenoid genes selected from the group consisting of *crtE*, *crtB*, *crtI*, *crtY*, and *crtW* of undefined structure from any source including variants, mutants and recombinants; and iv) to a method for preparing hydroxylated carotenoids by culturing said microorganism.

No information, beyond the characterization of for an isolated polypeptide of SEQ ID NO: 4 having β-ionone ring-2-hydroxylase activity and encoded by a polynucleotide sequence of SEQ ID NO: 3, isolated microorganism comprising said polynucleotide and encoding said polypeptide, said microorganism comprising carotenoid biosynthesis genes comprised in plasmids pAC-Cantha or pAC-Asta, comprising the polynucleotide coding sequences amplifiable from *Brevundimonas* sp. Strain SD-212 nucleic acid (DNA template) by primers comprising the following sequences: *crtE* (SEQ ID NO: 19 and 20), *crtB* (SEQ ID NO: 13 and 14), *crtI* (SEQ ID NO: 11 and 12), *crtY* (SEQ ID NO: 9 and 10) and *crtW* (SEQ ID NO: 7 and 8; page 20 of specification) and to a method for preparing hydroxylated carotenoids by culturing said microorganism, has been provided by the applicants, which would indicate that they had possession of the claimed genus of the polypeptides and encoding polynucleotides.

In the instant case, there is no structure associated with function recited with regard to the members of the genus of polypeptides and encoding polynucleotides, and the specification fails to provide any peptide consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a polynucleotide having a nucleotide sequence that hybridizes under defined stringent

conditions to a nucleotide sequence shown in SEQ ID NO: 3 or ii) any other carotenoid biosynthesis genes from any source including variants, mutants and recombinants and said microorganism is capable of introducing a hydroxyl group at the position 2 carbon of β-ionone ring.

Furthermore, neither the prior art at the time of filing of the instant application nor the specification provides information regarding catalytic domains, the binding domains, the core motifs and 3D model or the defined core regions/motifs involved in the desired biological activity/enzymological characteristics of the polypeptide i.e., β-ionone ring-2-hydroxylase activity, the tertiary structure of the molecule and folding patterns that are essential for the desired biological activity/enzymological characteristics. Therefore, examiner takes the position that due to the paucity of information regarding structure-function correlation, the specification lacks identifying characteristics of all of the sequences especially of any consisting of an amino acid sequence having a 50% or more identity with the amino acid sequence of SEQ ID NO: 4 and having β-ionone ring-2-hydroxylase activity and said peptide encoded by a polynucleotide having a nucleotide sequence that hybridizes under defined stringent conditions to a nucleotide sequence shown in SEQ ID NO: 3, within the claimed genus.

The genus of polynucleotides and encoded polypeptides required in the claimed invention is an extremely large structurally variable genus. While the argument can be made that the recited genus of polypeptides and encoding polynucleotides is adequately described by the disclosure of the structure of an isolated polypeptide of SEQ ID NO: 4 having β-ionone ring-2-hydroxylase activity and encoding polynucleotide

of SEQ ID NO: 3, since one could use structural homology to isolate those polynucleotides and encoded polypeptides recited in the claims. As taught by the art, even highly structurally homologous polynucleotides and encoded polypeptides do not necessarily share the same function i.e., conservation of structure is not necessarily a surrogate for conservation of function. For example, Witkowski et al., (Biochemistry 38:11643-11650, 1999), teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al., (J. Bacteriol., 183(8): 2405-2410, 2001), teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, the claimed genera of polypeptides and encoding polynucleotides include widely variable structure and associated functions, since minor changes in structure may result in changes affecting function and no additional information correlating structure with distinct enzymological characteristics has been provided.

Due to the fact that the specification only discloses an isolated polypeptide of SEQ ID NO: 4 having β-ionone ring-2-hydroxylase activity and encoded by a polynucleotide sequence of SEQ ID NO: 3, isolated microorganism comprising said polynucleotide and encoding said polypeptide and to a method for preparing

hydroxylated carotenoids by culturing said microorganism, and the lack of description of any additional species/variants/mutants/recombinants by any relevant, identifying characteristics or properties or structure-function correlationship for the recited β-ionone ring-2-hydroxylase, one of skill in the art would not recognize from the disclosure that applicant was in possession of the claimed invention.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In support of their request that the prior rejection of claims 1-8 and 18 under 35 U.S.C. 112 for written description be withdrawn, applicants' have provided a common line of argument for traversing enablement and written description.

"The specification on page 14 details other genes, which encode proteins having β-ionone ring-2-hydroxylase activity would have at least 50% homology to SEQ ID NO: 4 based on the comparison with other carotenoid proteins and this level of identity would be expected to be present in the enzymes encoded by genes isolated from other organisms)... Thus, the specification provides a detailed structure/function analysis..." (pages 10-11 of applicants' response dated 02/18/09).

Reply: Examiner's answer, rebutting the applicants' argument for maintaining the enablement rejection applies equally in maintaining the written description rejection. Examiner continues to hold the position that, the genus of peptides and encoding polynucleotides as recited in the claimed invention is an extremely large and structurally variable genus. Therefore, the claimed genera of peptides and encoding

polynucleotides include peptides having widely variable structures, since minor structural changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polynucleotides and encoded polypeptides are encompassed by these claims. The specification only discloses a single species within the recited genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Furthermore; 1) The key focus of the argument is on the claims as written (see *In re Hinkler* 150 F .3d 1362, 1369, 47 USPQ2d 1523 (fed. Cir. 1998) and not proffered facts and are not commensurate with the scope of claims and therefore unpersuasive.

2) Although the claims are examined in the light of the specification, specification cannot be read into the claims, i.e., the limitations of the specification cannot be read into the claims (see MPEP 2111 R-5).

415 F.3d at 1316, 75 USPQ2d at 1329. See also< In re Hyatt, 211 F.3d 1367, 1372,54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969) (Claim 9 was directed to a process of analyzing data generated by mass spectrographic analysis of a gas. The process comprised selecting the data to be analyzed by subjecting the data to a mathematical manipulation. The examiner made rejections under 35 U.S.C. 101 and 102. In the 35 U.S.C. 102 rejection, the examiner explained that the claim was anticipated by a mental process augmented by pencil and paper markings. The court agreed that the claim was not limited to using a machine to carry out the process since the claim did not explicitly set forth the machine. The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an

infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."). The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach.

For the above cited reasons, claims 1-8 and 18 are rejected under 35 U.S.C. 112, first paragraph for enablement and written description is maintained.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claim 18 is objected for abbreviation.

2) Claims 1-8 and 18 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement and written description.

Conclusion

None of the claims are allowable. Claims 1-8 and 18 are objected/rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ganapathirama Raghu/
Patent Examiner
Art Unit 1652